REMARKS

Initially, Applicants respectfully request that the Examiner provide a signed and initialed copy of the Form-1449 submitted with the June 6, 2003 Information Disclosure Statement. A copy of the 1449 is attached hereto for the Examiner's convenience.

Claims 27 and 29-32 are pending in the application.

The claimed invention is a culture device for inducing activation of immunosuppressive cells, wherein the culture device is coated with:

(1) the $F(ab)_2$ fragment of the anti-CD2 antibody TS2/18; and

(2) at least one anti-CD3 antibody.

I. Rejections Under 35 U.S.C. § 103(a)

(A) Claims 27, 29 and 30 remain rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,171,799 to Skibbens (hereinafter '799) in view of Schwarz *et al.* and Jones *et al.* The Examiner asserts that the '799 patent teaches a device for culturing immunosuppressive cells where the device is coated with the anti-CD3 antibody OKT3, Schwartz *et al.* teach the inhibitory effects of the anti-CD2 antibody TS2/18 on T cell activation, and Jones *et al.* teach that whole antibodies and $F(ab)_2$ fragments may be used interchangeably. The Examiner further contends that there is a motivation to combine the teachings of '799 with those of Schwartz *et al.* since it is *prima facie* obvious to combine two or more compositions that have the same purpose to create a third composition for the same purpose. The Examiner also contends that there is a motivation to combine the teachings of Jones *et al.* with those of '799 and Schwartz *et al.*, because Jones teaches that $F(ab)_2$ fragments are sometimes preferred over whole antibodies.

Applicants respectfully request reconsideration and withdrawal of this rejection on the following grounds.

For a *prima facie* case of obviousness, the Examiner must find all elements of the claimed invention in the teachings of the prior art along with a motivation to combine these teachings with a reasonable probability of success. Where such a *prima facie* case is made, Applicants may rebut a conclusion of obviousness by providing evidence of, *inter alia*, unexpectedly superior properties of the claimed invention.

First, Applicants assert that the Examiner has not made a *prima facie* case of obviousness of claims 27, 29, and 30 because there is no motivation to combine the teachings of '799 with those of Schwartz *et al.* Specifically, Applicants submit that OKT3 and TS2/18 are not used for the same purpose in the cited prior art, contrary to the Examiner's position. In '799, the anti-CD3 antibody OKT3 is used for its conventional purpose of stimulating and proliferating T cells (see column 33, lines 30 to 53, describing the culture of RA synovial tissue derived T cells on an OKT3-coated plate, and describing the proliferative response of PBLs to OKT3). On the other hand, Schwartz *et al.* teach that the anti-CD2 antibody TS2/18 inhibits tyrosine phosphorylation induced by an anti-CD3 antibody, and that anti-CD2 mAbs have the potential to inhibit activation of T cells (see page 5817, left column, lines 10 to 12, and second column, first line of discussion). Therefore, since the prior art indicates that anti-CD3 antibodies activate T cells while TS2/18 inhibits the activation thereof, anti-CD3 antibodies and TS2/18 function in the exact opposite manner according to the prior art. Consequently, claims 27, 29, and 30 are not obvious because one skilled in the art would not have been motivated to combine the teachings of `799 and Schwarz *et al.* to induce activation of immunosuppressive cells as claimed in the present application.

Further, Schwartz *et al.* teach away from a culture device coated with an anti-CD3 antibody and TS2/18, since Schwartz *et al.* teach that TS2/18 blocks signal transduction through CD3 (see page 5814, second paragraph), and more specifically, that TS2/18 inhibits tyrosine phosphorylation induced by cross-linked anti-CD3 mAbs (see page 5817, first paragraph). Therefore, one skilled in the art would have been motivated to not produce a culture device coated with both an anti-CD3 mAb and TS2/18, since, according to the prior art, TS2/18 will merely block the effects of the anti-CD3 antibody. Accordingly, claims 27, 29, and 30 are not obvious because Schwartz *et al.* teach away from the combination of an anti-CD3 mAb and TS2/18 in the presently claimed cell culturing device.

Even if the Examiner had made a *prima facie* case of obviousness, the presently claimed invention has unexpectedly superior properties sufficient to rebut the Examiner's obviousness rejection. Specifically, one skilled in the art would not have expected the superior properties of the present culture device obtained using the $F(ab)_2$ fragment of TS2/18. Such unexpectedly superior properties are evident in the specification by comparing the cells of (d) (e) and (f) in Example 1 (see pages 19-20 of the substitute specification and Figure 6). When an anti-CD3 antibody is used alone (as in the '799 patent), immunosuppression is approximately 50% (see Figure 6), and approximately 67% when an anti-CD3 antibody is used with the entire TS2/18 antibody. However, immunosuppression is approximately 78% when the $F(ab)_2$ fragment of TS2/18 and an anti-CD3 antibody are used simultaneously as claimed in the present application.

Such a result would have been unexpected given the teachings of the prior art. Jones *et al.* merely teach that, in enzyme immunoassays, false-positive reactions (i.e. non-specific interferences) tend not to occur with $F(ab)_2$ fragments. Jones *et al.* neither teach nor suggest that $F(ab)_2$ fragments of TS2/18 are superior over whole TS2/18 antibodies for culturing

immunosuppressive cells, as false-positive reactions in enzyme immunoassays are not relevant to culturing immunosuppressive cells. Consequently, one skilled in the art would not have expected the superior properties of using the $F(ab)_2$ fragment of TS2/18 over whole TS2/18 antibodies in a culture device for inducing activation of immunosuppressive cells, as claimed in the present Application.

For the reasons stated above, Applicants assert that claims 27, 29, and 30 are not obvious over '799 in view of Schwarz *et al.* and Jones *et al.*, and accordingly, Applicants respectfully request withdrawal of this rejection.

(B) Claims 27, 29 and 30 remain rejected under 35 U.S.C. § 103(a) as obvious and over E.P. 0421380A1 (EP'380), in view of Schwartz *et al.*, and further in view of Jones *et al.* The Examiner asserts that EP'380 teaches a culture device coated with both an anti-CD3 antibody and an anti-CD2 antibody, Schwartz *et al.* teach the anti-CD2 antibody TS2/18, and Jones *et al.* teach that $F(ab)_2$ fragments may be preferred in some cases to whole antibodies. The Examiner contends that the motivation to combine the teachings of the EP'380 patent with the teachings of Schwartz *et al.* stems from the fact that it would have been obvious to use the TS2/18 antibody of Schwartz as the anti-CD2 antibody of EP'380. The Examiner also contends that there is a motivation to combine the teachings of Jones *et al.* with those of '799 and Schwartz *et al.*, because Jones *et al.* teach that $F(ab)_2$ fragments are sometimes preferred over whole antibodies.

Applicants respectfully request reconsideration and withdrawal of the rejection on the following grounds.

Again, for a *prima facie* case of obviousness, the Examiner must find all elements of the claimed invention in the teachings of the prior art along with a motivation to combine these

teachings with a reasonable probability of success. Where such a *prima facie* case is made, Applicants may rebut a conclusion of obviousness by providing evidence of, *inter alia*, unexpectedly superior properties of the claimed invention.

First, Applicants submit that the prior art does not provide a motivation to combine the TS2/18 monoclonal antibody (as taught by Schwartz *et al.*) with an anti-CD3 monoclonal antibody (as taught by EP'380) to produce the presently claimed culturing device. The Examiner takes the position that the TS2/18 antibody of Schwartz *et al.* could be used as the anti-CD2 antibody suggested by EP'380 for enhancing activation of cytotoxic T cells. However, EP'380 teaches a device for inducing tumor-lysing cells with stimulants *in vitro* (see for example, page 1, paragraphs 4 and 5). One skilled in the art would not be motivated to include an immunosuppressive antibody such as TS2/18 in the device of EP'380, for it would be undesirable to include an immunosuppressive antibody in the device to activate immune cells toward tumors.

Even if the Examiner had made a *prima facie* case of obviousness, the presently claimed invention has unexpectedly superior properties sufficient to rebut the same. For reasons stated above, one skilled in the art would not have expected the superior properties of the present culture device coated with the $F(ab)_2$ fragment of TS2/18 as opposed to whole TS2/18 antibodies.

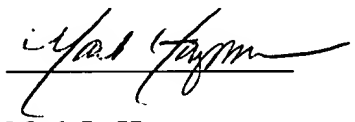
Accordingly, Applicants assert that claims 27, 29, and 30 are not obvious over EP'380, in view of Schwarz *et al.* and Jones *et al.*, and accordingly, Applicants respectfully request withdrawal of this rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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